
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): **March 3, 2009**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(IRS Employer Identification No.)

1896 Rutherford Road

Carlsbad, CA 92008

(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
 - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
 - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
 - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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Item 1.01. Entry into a Material Definitive Agreement.

On March 3, 2009, Regulus Therapeutics Inc. ("Regulus"), Alnylam Pharmaceuticals, Inc. ("Alnylam") and Isis Pharmaceuticals, Inc. ("Isis") executed a Series A Preferred Stock Purchase Agreement pursuant to which Regulus raised \$20 million in a Series A preferred equity financing. Alnylam and Isis were the sole and equal investors in the financing. Regulus was established in September of 2007 by Alnylam and Isis to focus on the discovery, development, and commercialization of microRNA-based therapeutics.

Regulus filed a press release describing this transaction. A copy of this press release is attached as Exhibit 99.1 to this Current Report and incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated March 4, 2009.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

INDEX TO EXHIBITS

99.1 Press Release dated March 4, 2009.



Contacts

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Regulus Therapeutics Receives \$20 Million in a Series A Equity Financing

The leading microRNA therapeutics company further strengthens balance sheet to advance programs towards the clinic

CARLSBAD, Calif., and CAMBRIDGE, Mass., March 4, 2009 — Regulus Therapeutics Inc., Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq:ISIS) announced today that Regulus has raised \$20 million in a Series A preferred equity financing that further strengthens its balance sheet. Alnylam and Isis were the sole and equal investors in the financing. Regulus was established in September of 2007 by Alnylam and Isis to focus on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus also announced that the company has completed a legal reorganization from an LLC to a C-Corporation providing an optimal capital structure for additional future investors.

“We are very pleased to further strengthen our balance sheet in the current difficult financial environment. This equity financing, when combined with last year’s significant upfront payment made by GlaxoSmithKline as part of our partnership, gives Regulus cash that we expect will last at least through 2011. In addition, the reorganization of our capital structure to a C-Corporation sets the basis for a strong, independent company allowing us to more flexibly attract capital and continue forging relationships with the pharmaceutical industry,” said Kleantlis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. “We have made significant scientific and business progress in a very short time, due in part to the support and expertise of Alnylam and Isis. We believe that Regulus remains at the very center of discovery and development of drugs targeting microRNAs, an entirely new frontier of pharmaceutical research leading to innovative medicines. Most recently, we demonstrated for the first time ever *in vivo* therapeutic efficacy by targeting a microRNA, miR-21, in an animal model of human

cardiac disease. Moreover, the continued expansion of our R&D programs highlights the breadth of opportunity for microRNA-based therapeutics.”

Regulus has a broad asset estate that includes dominant intellectual property with over 900 patents (approximately 600 issued and 300 pending), a solid understanding of microRNA biology, as well as unique proven chemistry and technological know-how to discover and develop oligonucleotide therapeutics targeting microRNAs.

“We are extremely pleased with the progress at Regulus as they explore a new and exciting target space with access to leading technologies and intellectual property from Isis and Alnylam,” said John Maraganore, Ph.D., Chairman of the Board of Regulus and Chief Executive Officer of Alnylam. “We continue to view microRNAs as a transformative discovery for the advancement of innovative medicines and are confident that Regulus will lead the discovery and development of microRNA therapeutics across the industry. Notwithstanding significant outside investor interest, we and Isis have jointly decided to continue to maintain our current ownership levels in Regulus in the best interests of our shareholders.”

“Over the past 18 months, Regulus has made significant progress across all areas of its business by achieving a significant partnership with GlaxoSmithKline, building a capable and entrepreneurial management team, and publishing ground-breaking research that demonstrates the therapeutic potential of microRNA-based drugs in many different disease areas,” said Stanley Crooke, M.D., Ph.D., Chairman, President and Chief Executive Officer of Isis. “We view this financing as our commitment to supporting Regulus as it translates one of the most important new discoveries in biology into a novel approach for treating disease, as the company advances as one of the biotechnology industry’s future leaders.”

The board of directors of Regulus will remain unchanged and will continue to include David Baltimore, Ph.D., Nobel Laureate and Prof. at Caltech, Stanley Crooke, MD, Ph.D., Chairman, President & CEO of Isis, Barry Greene, President & COO of Alnylam, John Maraganore, Ph.D., CEO of Alnylam and Chairman of the Board of Regulus, Stelios Papadopoulos, Ph.D., former Vice Chairman of Cowen and Co., B. Lynne Parshall, CFO & COO of Isis, and Kleantlis G. Xanthopoulos, Ph.D., President & CEO of Regulus.

About microRNAs

microRNAs are a recently discovered class of genetically encoded endogenous RNAs, approximately 20 nucleotides in length, that are believed to regulate the expression of a large number of human genes. microRNAs have been described as being involved in the regulation of gene expression as part of physiology and development. microRNA-based therapeutics represent a new approach for the treatment of a wide range of human diseases. The inappropriate absence or presence of specific microRNAs in various cells has been shown to be associated with specific human diseases including cancer, viral infection, cardiovascular, metabolic disorders and immuno-inflammatory disease. Targeting microRNAs with novel oligonucleotide therapeutic agents could result in novel and broadly acting treatments for a number of serious human diseases.

Regulus Therapeutics Inc is a biopharmaceutical company aiming to discover, develop, and commercialize microRNA-based therapeutics. Regulus aspires to translate one of the most important new discoveries in biology into a novel approach for innovative medicines and to build the leading microRNA company. Regulus was established by Alnylam Pharmaceuticals and Isis Pharmaceuticals in September of 2007 and benefits substantially from their RNA therapeutic drug discovery expertise, unique and established oligonucleotide-based technologies, and a broad and dominant intellectual property estate specific to microRNA-based therapeutics. Regulus' patent estate includes over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNA for therapeutic applications. In addition, through its numerous collaborations with academic researchers, Regulus continues to expand its knowledge on the biological role of therapeutically relevant microRNAs. In April 2008, Regulus formed a major alliance with GlaxoSmithKline to explore microRNA therapeutics for immuno-inflammatory diseases. Regulus maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.com.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including *Nature*, *Nature Medicine*, and *Cell*. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection and is partnered with Cubist and Kyowa Hakko. In addition, the company is developing RNAi therapeutics for the treatment of a wide range of disease areas, including liver cancers, hypercholesterolemia, Huntington's disease, and TTR amyloidosis. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko, and Cubist. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam established "RNAi 2010" in January 2008 which includes the company's plan to significantly expand the scope of delivery solutions for RNAi therapeutics,

have four or more programs in clinical development, and to form four or more new major business collaborations, all by the end of 2010. Alnylam and Isis are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development, and commercialization of microRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

Forward-Looking Statement

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis', Alnylam's and Regulus' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus. Any statement describing Isis', Alnylam's or Regulus' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as such parties' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Such parties' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause their results to differ materially from those expressed or implied by such forward-looking statements. Although these forward-looking statements reflect the good faith judgment of the management of each such party, these statements are based only on facts and factors currently known by Isis, Alnylam or Regulus, as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis', Alnylam's and Regulus' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2008, and in Alnylam's annual report on Form 10-K for the year ended December 31, 2008, which are on file with the SEC. Copies of these and other documents are available from Isis or Alnylam.
